REMARKS

INTRODUCTION:

In accordance with the foregoing, claims 1, 6, 10, 14 and 19 have been amended, and claim 13 has been canceled without prejudice or disclaimer. No new matter is being presented, and approval and entry are respectfully requested.

Claims 1-12 and 14-20 are pending and under consideration. Reconsideration is respectfully requested.

REJECTION UNDER 35 U.S.C. §103 AND EXAMINER'S RESPONSE TO APPLICANTS' RESPONSE FILED OCTOBER 15, 2007:

In the Office Action, at page 2, claims 1-9 were rejected under 35 U.S.C. §103(a) as being unpatentable over Peverali et al. (USPN 6,518,456; hereafter, Peverali) in view of Cannata et al. (U.S. Patent Publication 2004/0068011; hereafter, Cannata) for the reasons of record as set forth in the previous office action. Amended claims 10-12 and newly added claims 13-20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Peverali in view of Cannata for the same reasons as in the previous office action. In the Office Action, at pages 3-6, the Examiner presented her arguments in response to Applicants' Amendment filed October 15, 2007. The rejections are traversed and reconsideration is requested.

Independent claims 1, 10 and 19 have been amended to recite that the resulting solution obtained from mixing an aqueous solution of Gabapentin hydrochloride in water with an aqueous solution of an alkali metal base is heated to a temperature in the range of 60 -90 degrees C. These amendments are supported by Examples 1-10.

In addition, independent claims 1, 10 and 19 have been amended to recite: "wherein the Gabapentin has a chloride content of 100 ppm or less." These amendments are supported, for example, by claim 13, which has been canceled without prejudice or disclaimer.

It is respectfully submitted that Peverali teaches a stepped process by

1. refluxing 2-aza-spiro[4.5]decan-3-one ("lactam"), for a given time, in a hydrochloric acid aqueous solution. A first crop, obtained upon cooling, is recovered by filtration; the mother liquors are then concentrated to obtain further crops. The recovered product has high purity and contains small amounts of the starting "lactam", moreover the recovery yield is higher than 85% (Example 1)
2. Crude gabapentin hydrochloride is digested in acetone to remove hydrochloric acid, while further reducing the amount of "lactam" still present. The hemihydrate

hydrochloride is obtained after drying. (Example 2)

3. Gabapentin is obtained by treating a hot concentrated aqueous solution of gabapentin hydrochloride with sodium hydroxide to the amino acid isoelectric point, then cooling and filtering the precipitated gabapentin, which is washed with an ethanol/water mixture thereby obtaining a product with sodium chloride content even lower than 1%. The mother liquors are concentrated to obtain further crops, until a 90% overall yield. (Examples 3 & 6)

4. Gabapentin is crystallized from deionized water, further reducing the content of inorganic salts still present. (Example 4)

5. Crystallization from water is not always necessary, in that sodium chloride concentration can be brought below 0.02% (corresponding to Cl ion.≤ 0.01%) by hot digestion in an ethanol/isopropyl ether or methanol/isopropyl ether mixture. The mixture is then cooled, filtered and dried to obtain almost quantitatively highly pure, anhydrous gabapentin having low content in inorganic salts. (example 5 and 7, 8, 9 & 10)

The above process steps are different from the process of independent claims 1, 10 and 19 of the present invention. Examples 1 and 2 of Peverali teach steps to prepare and purify gabapentin hydrochloride after digestion of crude gabapentin hydrochloride in acetone, which is used in Examples 3 and 6 to prepare gabapentin. Peverali teaches two examples (Examples 3 and 6) of preparing crude gabapentin. Peverali teaches, in Examples 3 and 6, that the resulting solution obtained from mixing an aqueous solution of Gabapentin hydrochloride in water with an aqueous solution of an alkali metal base is heated to a temperature in the range of 50-60 degrees C; thus, in Example 3, a 68.9% yield of crude gabapentin is obtained with a first crop having 0.22% NaCl (2200 ppm NaCl= 1327 ppm Cl^-) and a second crop having 0.8% NaCl (8000 ppm NaCl= 4827 ppm Cl^-). In Peverali's Example 6, a 66.4% yield of crude gabapentin is obtained with a first crop having 0.06% NaCl (600 ppm NaCl= 362 ppm Cl^-), and a second crop having 1.5% NaCl (15000 ppm NaCl= 9051 ppm Cl^-).

Examples 4 and 5 of Peverali teach further steps to purify the crude gabapentin of Example 3. Upon purification using Examples 4 and 5, a net yield of 60.8% gabapentin is obtained, and the NaCl content is reduced to 0.006% (60 ppm NaCl = 36 ppm Cl^-).

Examples 7-10 teach further steps to purify the crude gabapentin of Example 6. Upon purification using Examples 7-10, a net yield of 80.7 % is obtained, and the NaCl content is reduced to 0.013% (130 ppm NaCl= 78 ppm Cl^-).

Hence, Peverali requires the further steps of Examples 4 and 5 or else 7 or 8 and 9-10 to

obtain gabapentin which is competitively pure with the gabapentin of amended independent claims 1, 10 and 19 of the present invention.

Peverali specifically teaches the removal of hydrochloric acid and lowering of lactam content in gabapentin hydrochloride itself by digestion of the crude gabapentin hydrochloride in acetone (col 2, lines 25-20 and claim 1 (b)). In the present invention there is no such step of digestion in acetone. In fact, there is no use of acetone in any step of the process of the present invention. Thus, Peverali teaches away from the present invention. A person skilled in the art would be motivated to first digest the gabapentin hydrochloride in acetone prior to the hydrolysis in order to achieve lower hydrochloride and to reduce the gabalactam content. Surprisingly, the applicants are able to achieve low chloride and lactam content without digesting gabapentin hydrochloride in acetone.

The Examiner has cited Example 8 of Peverali (the product obtained through example 1, 2 and 6) as disclosing gabapentin with chloride content much less than 100ppm; specifically it mentions the chloride content as 0.007% which is equivalent to 42ppm. A careful analysis of the said example would reveal that the example involves the crystallisation (digestion) of gabapentin in methanol/diisopropyl ether which is completely different from the solvent system of isopropyl alcohol, methanol and water in a ratio ranging from 4.54-19.64: 3.88-15.64: 1 as employed in the present invention. In fact, Peverali is completely silent on the use of the isopropyl alcohol, methanol and water for recrystallisation of crude gabapentin.

The applicants reiterate that the process of the present invention is not the same as the process as disclosed in Peverali. In fact, the present process completely avoids the step of digestion of crude gabapentin hydrochloride while still being successful in achieving the desired pure Gabapentin meeting the stringent pharmaceutical specifications in lesser number of steps than the steps as taught by Peverali.

The terminology "consists essentially of" is submitted to disallow ethanol recrystallization to form the gabapentin hydrochloride hemihydrate. Thus, independent claims 1, 10 and 19, respectively, and the claims depending therefrom, are submitted not to read on a process to form the hemihydrate in the synthesis of gabapentin from gabapentin hydrochloride.

As is stated in the Abstract of Cannata, recited below for the convenience of the Examiner, Cannata teaches the use of a cationic ion exchange resin to purify gabapentin:

> A process for the purification of gabapentin by treatment of a crude aqueous gabapentin hydrochloride solution with a strong cationic ion exchange resin. (emphasis added)

Cannata does not teach the present invention. Instead, Cannata uses a resin. Hence, it is respectfully submitted that there is no reason submitted by the Examiner for combining Cannata with Peverali.

Also, it is respectfully submitted that there must be a reason for one of skill in the art to make the claimed combination, i.e., it is submitted that it remains necessary to identify some reason that would have led a chemist to modify a process in a particular manner to establish prima facie obviousness of a new process.

Further, it is respectfully submitted that the rejection utilizing Cannata is being based, in part, on the personal knowledge of the Examiner, i.e., the assumption that water would be present in the alcohol solutions and/or that an ion exchange conversion process would be applicable to a process that does not utilize same. The personal knowledge of the Examiner, when used as a basis for a rejection, must be supported by an affidavit as to the specifics of the facts of that knowledge when called for by the applicant. See, MPEP 2144.03, 37 C.F.R. § 1.104(d)(2). In short, the rules of the U.S. Patent and Trademark Office require that the Examiner must either support this assertion with an Affidavit, or withdraw the rejection. Therefore, it is respectfully requested that the Examiner support the rejection with either an Affidavit or a reference, or withdraw the rejection with respect to Cannata.

For further clarification, the following comments are provided. The Applicants' invention relates to a process for the preparation of gabapentin involving the steps of:

(i) preparing an aqueous solution of gabapentin hydrochloride in water,

(ii) preparing an aqueous solution of an alkali metal base,

(iii) adding the aqueous solution of an alkali metal base to the aqueous solution of gabapentin hydrochloride,

(iv) heating the resulting solution gradually to a temperature in the range of 60 -90 deg C;

(v) obtaining a precipitate and separating the precipitate from its mother liquor, and

(vi) recrystallising the precipitate from a mixture of isopropyl alcohol, methanol & water in a ratio ranging from in a ratio ranging from 4.54-19.64: 3.88-15.64: 1 (v/v) to get gabapentin of over 99.5 % purity and another mother liquor, wherein Gabapentin has a chloride content of 100 ppm or less.

The basis for the ratio range 4.54-19.64: 3.88-15.64: 1 (v/v) of isopropyl alcohol, methanol and water is supported by the range of values for isopropyl alcohol, methanol and water set forth in Examples 1-10 in paragraphs [0074]-[0083] of the published application. The ratios are computed below for the Examiner's convenience:

Example No.	ml of isopropyl alcohol (IPA)	ml of methanol	ml of water (H_2O)	IPA:Methanol:H_2O
1	815	80+570 = 650	16+60= 76	10.72: 8.55: 1
2	275	27+192= 219	3+11= 14	19.64: 15.64: 1
3	174	20+145= 165	6+23= 29	6: 5.68: 1
4	360	33+240= 273	8+30= 38	9.47: 7.18: 1
5	116	25+174= 199	5+20= 25	4.64: 7.96: 1
6	360	50+360= 410	5.5+21= 26.5	13.58: 15.47: 1
7	500	86+625= 711	13+50= 63	7.93: 11.28: 1
8	260	3.6+260= 263.6	9+36= 45	5.77: 5.85: 1
9	370	52+370= 422	12+45= 57	6.49: 7.40: 1
10	600	63+450= 513	27+105= 132	4.54: 3.88: 1

Figures have not been rounded off.

In comparison Peverali discloses a process for the preparation of gabapentin, involving the steps of:

(i) hydrolyzing gabalactam with diluted aqueous HCl to recover gabapentin hydrochloride

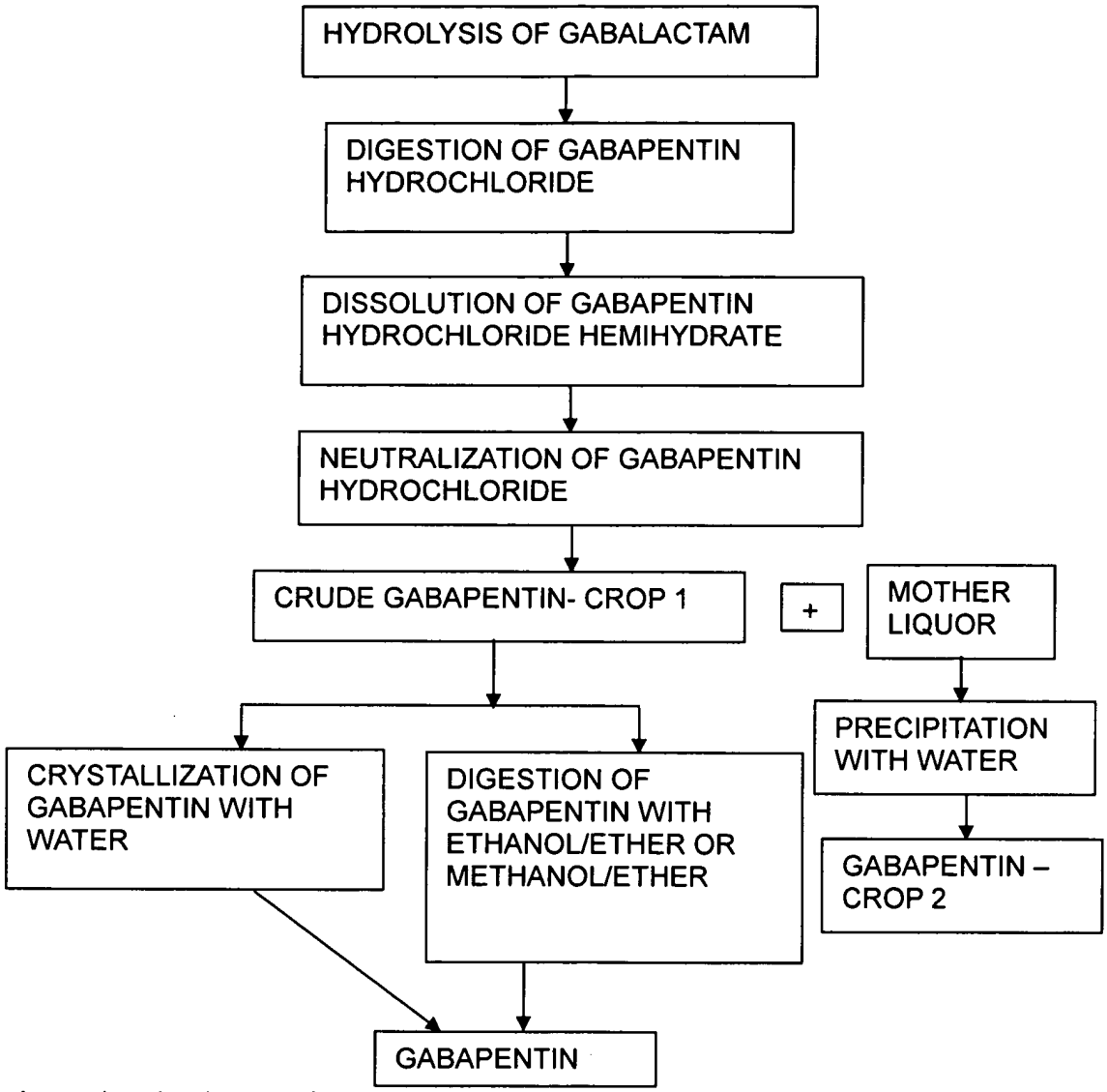
(ii) digesting with acetone to remove residual hydrochloric acid,

(iii) dissolving gabapentin hydrochloride hemihydrate in water and neutralizing with a base to reach the isoelectric point (pH 7.1-7.2), and

(iv) crystallizing gabapentin from deionized water; or, alternatively digesting the hot gabapentin in ethanol/diisopropyl ether or methanol/diisopropyl ether.

In a comparison of the Applicants' application with the invention of Peverali, the following can be inferred: In the Peverali process, initially a purification step of gabapentin hydrochloride is adopted, wherein the impure gabapentin hydrochloride is digested in acetone to remove the lactam and excess hydrochloric acid and to obtain gabapentin hemihydrate. In contrast, in the Applicants' process, no such purification of gabapentin hydrochloride is adopted. Instead, in the Applicants' process, gabapentin hydrochloride (as compared with the gabapentin hydrochloride hemihydrate of Peverali) is dissolved directly in water without resorting to purification of gabapentin hydrochloride, as is done in the case of Peverali, which has resulted in gabapentin hydrochloride hemihydrate.

To aid in the comparison of Peverali with the present application, the process steps of Peverali are now depicted in the form of a flow chart, which is derived from Examples 1-9.



It can be clearly seen from the process steps that, subsequent to the basification of the aqueous solution of gabapentin hydrochloride hemihydrate, crop 1 of crude gabapentin is obtained. The crop 1 is then crystallized in two alternate steps as stated below;

Alternate Step 1

The crop 1 of gabapentin is treated with water (as a solvent) to obtain a crystallised gabapentin. (Example 4)

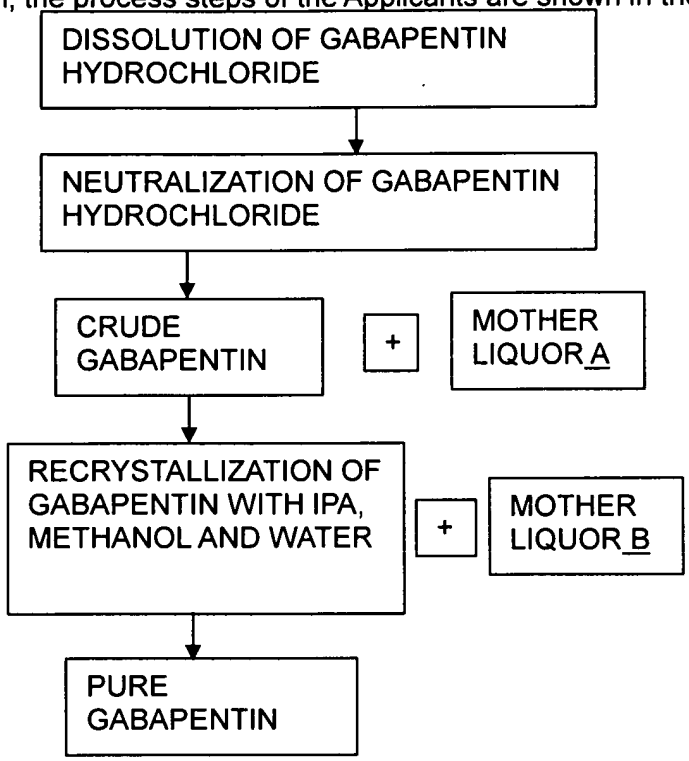
Alternate Step 2

The crop 1 of gabapentin is treated with a solvent system in a combination of ethanol and

ether or in a combination of methanol and ether to obtain a crystallised gabapentin. (Examples 7 & 8).

It can also been seen from the process steps of Peverali that, in addition to the performance of crystallization steps, Peverali also performs additional steps in obtaining crop 2 from the mother liquor. The mother liquor is further treated with water to obtain crop 2. Crop 2 is subjected to crystallization steps as mentioned above to obtain crystallised gabapentin.

In comparison, the process steps of the Applicants are shown in the following diagram:



In the Applicants' process, the basified gabapentin hydrochloride is recrystallised from a solvent system of isopropyl alcohol, methanol and water in a ratio ranging from 4.54-19.64 : 3.88-15.64 : 1 (v/v) to obtain gabapentin and another mother liquor. The mother liquor is further treated with aqueous sodium hydroxide to obtain gabalactam.

Therefore, it is clear that Applicants' process provides a single recrystallisation step of the crude gabapentin to obtain pure gabapentin.

Further, Peverali discloses a process wherein the crude gabapentin obtained is said to be form III (Example 4 & 9) or form II (Example 6) which, when recrystallised, is converted to pure gabapentin of form II, which is the pharmacopoeial material. In comparison, the Applicants' process discloses crude gabapentin obtained as form I, and after recrystallisation, the pure gabapentin obtained is form II.

In reply to the Examiner's response on chloride content present in gabapentin obtained in Example 8 of Peverali, which corresponds to 0.007% NaCl or 42 ppm of Cl^- (column 6, line 46)

having the HPLC purity 100% with the lactam concentration lower than detectable, it is submitted that a careful analysis reveals that the first crop of crude gabapentin obtained in Example 6, containing 0.06% as NaCl (362 ppm Chloride content) and the second crop containing 1.50% as NaCl (9051 ppm Chloride content) are treated in two steps, namely, the digestion of the first crops in Example 8, and secondly, the crystallization of the second crops of crude gabapentin in Example 9. It is only in Example 8, when the first crops of the crude gabapentin are digested in methanol-diisopropyl ether, that the lactam content and the chloride content are low. For the second crops that are crystallized in Example 9, the lactam content is 0.26% and 0.014% NaCl (84 ppm Cl^-). It is therefore clear from the material of the first and the second crops that the purification of the gabapentin is performed in multiple steps. In contrast, the Applicants' process yields pure gabapentin with less chloride content, in fewer steps.

Cannata uses methanol and isopropanol to recrystallise the Gabapentin, while in the Applicants' process, a substantial volume of water is used in addition to methanol and isopropanol.

It is the submission of the Applicants that since, no percentage or other concentration of the reagents is mentioned in Cannata, it is assumed that the reagents used in the process are solvent grade methanol and solvent grade isopropanol. It is brought to the Examiner's kind notice that the concentration of solvent grade methanol from various manufacturers ranges from 99.8 to 99.9 %. Example 1 in Cannata uses 95 kg of methanol [Para 0028] which would correspond to approximately 1.2L of water in over 120 L of methanol, if the methanol is 99% pure. Similarly for concentration of solvent grade isopropanol ranges from 99.5 to 99.7%. Thus, the content of water, even if assumed to be present in the recrystallisation step in Cannata, would be very low.

However, in the Applicants' process water is added over and above the water (if any) already present in methanol and isopropanol solvents. Thus, even assuming that the process in Cannata does possess some content of water, it is negligible, and Cannata is completely silent about the use of water in the purification of crude gabapentin.

In contrast, in the Applicants' process, the amount of water used is substantially higher. In fact, the addition of water in the Applicants' process has unexpected advantages. The first advantage of the addition of water is that it increases the solubility of Gabapentin, and thus, brings down the volumes in the critical crystallization step (3 to 3.9 volumes), which is advantageous in production. An additional beneficial effect of adding water is that undesired polar impurities in the crude gabapentin are removed in this process of recrystallization. The chloride in the final product is reduced to less than 100 ppm.

Further, surprisingly the use of the solvent system of isopropanol, methanol and water in a ratio ranging from 4.54-19.64 : 3.88-15.64 : 1 (v/v) instead of employing methanol and isopropyl alcohol solvents as disclosed in Cannata, yields gabapentin which is not obtained in the form of a hydrate or a mixture thereof.

Hence, it is respectfully submitted that amended independent claims 1, 10 and 19 of the present invention are patentable under 35 U.S.C. §103(a) over Peverali in view of Cannata. Since claims 2-9, 11-12, and 14-20 depend from amended independent claims 1, 10 and 19, respectively, claims 2-9, 11-12, and 14-20 are patentable under 35 U.S.C. §103(a) over Peverali in view of Cannata for at least the reasons amended independent claims 1, 10 and 19 are patentable under 35 U.S.C. §103(a) over Peverali in view of Cannata.

CONCLUSION:

In accordance with the foregoing, it is respectfully submitted that all outstanding objections and rejections have been overcome and/or rendered moot, and further, that all pending claims patentably distinguish over the prior art. Thus, there being no further outstanding objections or rejections, the application is submitted as being in condition for allowance which action is earnestly solicited. At a minimum, this Amendment should be entered at least for purposes of Appeal as it either clarifies and/or narrows the issues for consideration by the Board.

If the Examiner has any remaining issues to be addressed, it is believed that prosecution can be expedited and possibly concluded by the Examiner contacting the undersigned attorney for a telephone interview to discuss any such remaining issues.

If there are any underpayments or overpayments of fees associated with the filing of this Amendment, please charge and/or credit the same to our Deposit Account No. 19-3935.

Respectfully submitted,

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